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Asymmetric Diels-Alder Reaction by the Use of a Chiral Titanium Catalyst with Molecular Sieves 4A. Remarkable Solvent Effect on the Enantioselectivity

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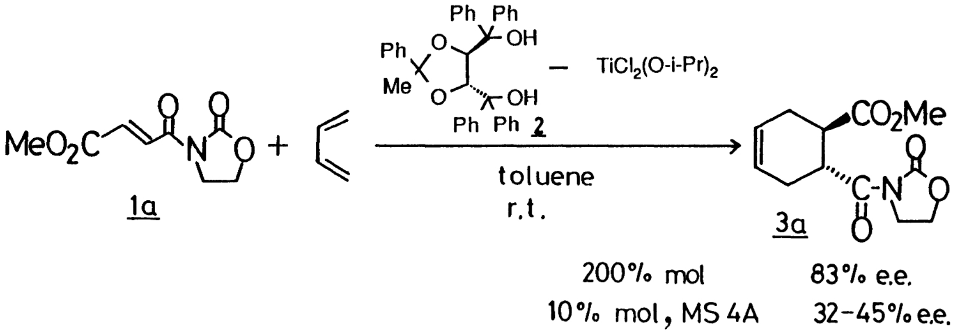
A remarkable effect of solvent on the enantioselectivity was observed in the asymmetric Diels-Alder reaction of 3-(2-alkenoyl)-1,3-oxazolidin-2-ones and dienes catalyzed by a chiral titanium reagent, and the Diels-Alder adducts were obtained in high enantioselectivity when alkyl-substituted benzenes were employed as the solvent.

Previously we reported that the asymmetric Diels-Alder reaction between 3-(2-alkenoyl)-1,3-oxazolidin-2-ones (1) and cyclopentadiene proceeds efficiently by the combined use of a catalytic amount of a chiral titanium alkoxide, which is prepared from the chiral 1,4-diol 2 and dichlorodiisopropoxytitanium(IV), in the presence of Molecular Sieves 4A (zeolite) to afford the corresponding Diels-Alder adducts in good enantioselectivity.[1)] In order to expand the utility of this reaction, we next examined the reactions of a fumaric ester derivative and acyclic dienes, which give synthetically useful cyclohexane dicarboxylic acid derivatives. However, compared with the reactions carried out in the presence of excess amounts of the chiral titanium reagent,[2)] this catalytic process gives poorer results in these cases. For example, the Diels-Alder adduct of the fumaric ester derivative of 1,3-oxazolidin-2-one 1a and butadiene was obtained in only 32-45% e.e.,[3)] as against 83% e.e. when two molar amounts of the chiral titanium alkoxide was used. In order to achieve the wide applicability of this catalytic procedure, the reaction conditions were examined in detail.



The reaction of the 1,3-oxazolidin-2-one derivative of fumaric ester **1a** and butadiene was examined in various solvents in the presence of a 10% molar amount of the chiral titanium alkoxide and powdered Molecular Sieves 4A. The typical experimental procedure was as follows: The chiral titanium alkoxide (ca. 0.05 M toluene solution) was prepared simply by mixing equimolar amounts of the chiral diol **2** and dichlorodiisopropoxytitanium(IV) in toluene. To a toluene (4 ml) suspension of powdered Molecular Sieves 4A (ca. 120 mg) were added the above toluene solution of the titanium alkoxide (0.1 mmol), a toluene solution (8 ml) of **1a** (1 mmol) and 1,3-butadiene (ca. 1 g), and the reaction mixture was stirred at room temperature.

The enantioselectivity displayed by the reactions in various solvents are summarized in the following table. It was noted that the enantioselectivity is influenced strongly by the solvent, and that alkyl substituted benzenes are very suitable solvents for the present reaction. The enantioselectivity is dependent on the number of methyl groups on the benzene ring and the optical purity of the adduct **3a** was greatly increased in the order of toluene, xylenes,and trimethylbenzenes(TMB). Furthermore, rather high enantioselectivity was attained by employment of hexylbenzene as the solvent, and the trans-4-cyclohexene-1,2-dicarboxylic acid derivative **3a** was obtained in 98% yield with 85% e.e.

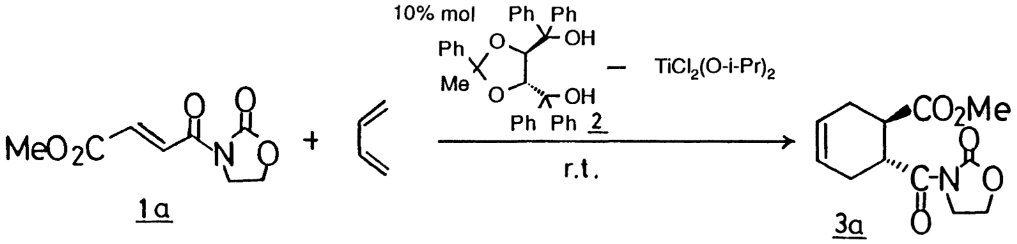


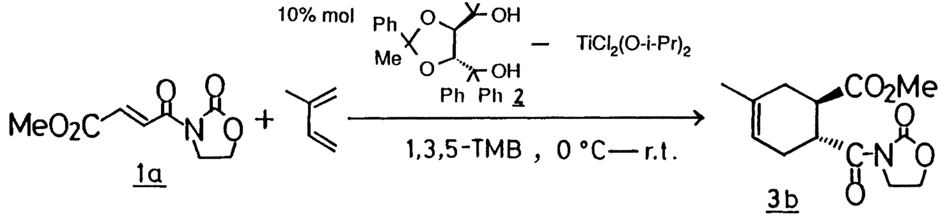
Table 1. Enantioselectivity in the Diels-Alder reaction of **1a** and butadiene

Solvent	%e.e.[a]	Solvent	%e.e.[a]
Benzene	22	CCl_4	58
Toluene	32-45	1,2,3-TMB[b]	77
o-Xylene	67	1,3,5-TMB	81
p-Xylene	68	1,3,5-TIPB[c]	85
Cumene	74	Hexylbenzene	85

a)Optical purity of the product was determined by the measurement of NMR spectrum of the corresponding dimethyl ester ($Mg(OMe)_2$/MeOH) using $Eu(hfc)_3$ as chiral shift reagent. The -OMe signal separates completely. In every case, the adduct had 1R,2R absolute configuration, which was determined by the optical rotation of the dimethyl ester.[5)]

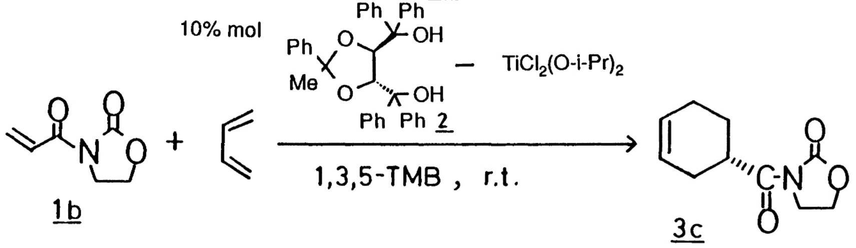
b)TMB : trimethylbenzene. c)TIPB : triisopropylbenzene.

The generality of the solvent effect on the enantioselectivity was examined in the following several examples using 1,3,5-trimethylbenzene (1,3,5-TMB) as the common solvent (under unoptimized reaction conditions). Reaction of **1a** with isoprene was also found to proceed smoothly in 1,3,5-TMB to afford the 4-methylcyclohexene-1,2-dicarboxylic acid derivative **3b** in 92% e.e.[4)]



99% yield, 92% e.e.
(in toluene, 61% e.e.)

An example of the solvent effect is also seen in the reaction of 3-acryloyl-1,3-oxazolidin-2-one (**1b**) which did not give sufficient asymmetric induction by the previous method.[1)] The reaction of **1b** with butadiene in 1,3,5-TMB gives the 3-cyclohexenecarboxylic acid derivative **3c** in 77% optical purity.[6)]



62% yield, 77% e.e.
(in toluene, 67% e.e.)

The reactions of various 3-(3-substituted acryloyl)-1,3-oxazolidin-2-ones **1c-e** with cyclopentadiene were found to proceed with higher asymmetric induction by using 1,3,5-TMB as the solvent, as compared with the results of the reactions in toluene, and the corresponding endo-adducts **3d-f** are prepared in 75-90% e.e.

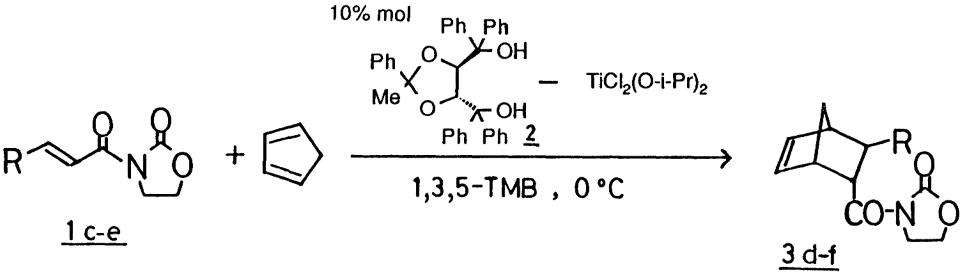


Table 2. Reactions of **1c-e** and cyclopentadiene

Dienophile		Yield/% (endo:exo)	Product	%e.e.[7)]
1c	R = Me	90 (91 : 9)	**3d**	91
1d	Ph	97 (92 : 8)	**3e**	82
1e	n-Pr	75 (91 : 9)	**3f**	75

As shown by the above results, the chiral titanium catalyst-Molecular Sieves 4A system is widely applicable to the reactions of a variety of dienophiles and dienes when a suitable alkyl substituted benzene is employed as a solvent, and synthetically important Diels-Alder adducts are prepared in high optical purities by the present catalytic process.

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References

1) K. Narasaka, M. Inoue, and T. Yamada, Chem. Lett., 1986, 1967: Asymmetric Diels-Alder reactions catalyzed by a chiral Lewis acid; see the references cited in the Ref. 2: Very recently, the asymmetric Diels-Alder reactions catalyzed by chiral titanium and aluminum reagents have been reported by Chapuis, Seebach, and Yamamoto, respectively; C. Chapuis and J. Jurczak, Helv. Chim. Acta, 70, 436 (1987); D. Seebach, A. K. Beck, R. Imwinkelried, S Roggo, and A. Wonnacott, Helv. Chim. Acta, in press; K. Maruoka, T. Ito, and H. Yamamoto, 54th National Meeting of the Chemical Society of Japan, Tokyo, April (1987), Abstr., No. 2 III M 14.

2) K. Narasaka, M. Inoue, and N. Okada, Chem. Lett., 1986, 1109.

3) The influence of sulfur contaminants in toluene was excluded by purifying toluene according to the procedure described in "Purification of Laboratory Chemicals," Pergamon Press, Oxford (1980).

4) Compound 3b was recrystallized from ethyl acetate-hexane several times to show the constant optical rotation ($[\alpha]_D^{25}$ -173° (c 1.0, CH_2Cl_2)). The optical purity of the product was determined based on this rotation. 3b was further converted to the corresponding dimethyl ester whose optical rotation ($[\alpha]_D^{22}$ -137° (c 1.2, $CHCl_3$)) coincided with the literature value.5)

5) H. M. Walborsky, L. Barash, and T. C. Davis, Tetrahedron, 19, 2333 (1963).

6) The optical purity and the absolute stereochemistry was determined by the optical rotation of the corresponding alcohol ($[\alpha]_D^{22}$ -77° (c 3.1, MeOH)) prepared by the reduction of 3c with $LiAlH_4$; S.Masamune, L. A. Reed III, J. T. Davis, and W. Choy, J. Org. Chem., 48, 4441 (1983); O. Ceder and B. Hansson, Acta Chem. Scand., 24, 2693 (1970).

7) The products were reduced to alcohols with $LiAlH_4$, and the optical purity was determined by HPLC analysis of the corresponding chiral Pirkle's carbamate.8) The absolute stereochemistry of **3d** was determined to be 5S,6R as shown in the scheme by the method described in Ref. 2, and those of **3e** and **3f** were not rigorously assigned.

8) W. H. Pirkle and M. S. Hoekstra, J. Org. Chem., 39, 3904 (1974).

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